Modern Concepts of Cardiovascular Disease

Published monthly by the AMERICAN HEART ASSOCIATION

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

DR. J. HAMILTON CRAWFORD, Brooklyn, *Editor*

DR. CHARLES A. POINDEXTER, New York, *Associate Editor*

Vol. XIII **June, 1944** **No. 6**

SCHOOL OF MEDICINE MEMORIAL LIBRARY

CHEMICAL CHANGES IN THE MYOCARDIUM IN DISEASES INVOLVING THE HEART

The human heart has received much attention at the hand of the pathologist and the physiologist but relatively little attention from the biochemist. A chemical mechanism supplies the energy for the muscular work which the heart performs. When a breakdown occurs in the ability to convert chemical energy into mechanical energy the heart fails. While we do not yet fully understand the processes involved we do know some of the important key factors, and these probably furnish an index to the state of this chemical mechanism.

With the discovery of phosphocreatine and adenosinetriphosphate, our theories regarding the energetics of muscular activity have been entirely changed. It would appear that these phosphorous compounds serve as intermediaries in the transfer of chemical energy to the mechanical energy of the heart beat. It seems probable that the organic phosphoric acid compounds exist as potassium salts and account for most of the intracellular potassium. If these premises are correct the concentration of these compounds in the myocardium should serve as an index of the potential capacity of the heart for work. Phosphocreatine is such a labile compound that it is impossible to determine it in the human heart at autopsy. However, variations in creatine are probably equally significant. The concentration of creatine, purine nitrogen, phosphorus and potassium in the left and right ventricular muscle of the normal heart and the heart in disease, especially in hypertrophy and failure will be compared and discussed chiefly on the basis of data collected by Mangun and the writer.

The creatine content of human heart muscle has been studied by Cowan, Herrmann and his coworkers, and the writer and his associates. The significance of potassium in congestive heart failure received attention from the medical group at Vanderbilt several years ago. The writer[1] has already reviewed the literature on this general problem and it will not be cited again here, although it might be noted that Gross and Sanberg[2] have since reported additional observations on the creatine concentration of the human heart.

Before making deductions regarding pathological changes it is obviously necessary to secure strictly normal data for comparison, and these have been obtained from the heart and voluntary muscle of 13 individuals dying accidental deaths. From the average data presented in Table I, it will be observed

TABLE I

Observations on the Heart and Voluntary Muscle of 13 Normal Human Subjects (mg. per 100 gm. of wet tissue)

	Left Ventricle	Right Ventricle	Voluntary Muscle
Creatine	203	165	443
Phosphorus	194	160	201
Potassium	285	219	328
Water	80.8	82.3	76.2
Fat	0.35	1.28	1.68

that the creatine, phosphorus and potassium are appreciably higher in the left than in the right ventricle, but that the water and fat are higher in the right ventricle. This also appears to be true for connective tissue in the right ventricle. When allowance is made for the difference in the extracellular water, the fat and connective tissue, the difference between the two ventricles is relatively small.

The question may be asked whether the changes observed in the wet muscle of pathological hearts are not due largely to changes in water, connective tissue and fat. Recalculation of our figures on the basis of water and fat free tissue, however, did not eliminate the very definite changes which occur in heart failure. On this account we have continued to record our findings on the basis of wet tissue, since this is the condition in which the heart functions.

Before attempting to analyze the changes which can occur in the creatine concentration of pathological hearts, it will be helpful to consider the changes which occur in the creatine content of voluntary muscle in disease and the possible influence of these diseased conditions upon the creatine content of the heart. In uremia and fevers the creatine values of voluntary muscle tend to be elevated and range from 400 to 560 mg. per 100 gm. (in comparison with the normal of 443 mg.), while in such conditions as carcinoma and diabetes the concentration is definitely lowered — may reach 300 mg. In studying our data on the creatine content of the left and right ventricles in comparison with that on the voluntary muscle, it was observed that when the creatine content of the voluntary muscle exceeded the normal in uremia or pneumonia this was accompanied by correspondingly high values in the left ventricle, and also in the right ventricle in uremia, but not in pneumonia. In diabetes, on the other hand, the creatine of the right ventricle is definitely lowered, although the creatine content of the left ventricle is essentially normal despite the marked fall in the voluntary muscle.

The question of the effect of cardiac hypertrophy upon the chemical composition of the human heart is of importance both as a phenomenon in itself and in relation to myocardial failure. It would appear that cardiac hypertrophy is intimately associated with failure and may possibly be the principal factor in bringing about an eventual breakdown in the metabolic transfer between the blood and muscle required to keep pace with the increased demands upon the energy output. Wearn[3] has shown that as a result of the increase in diameter of the muscle fibers in hypertrophy there is a decrease in the number of capillaries per sq. mm. of heart muscle. This ultimately leads to a considerable increase in the radial distance the metabolites must diffuse from each capillary, a situation which may conceivably lead to decreased nutrition and anoxia of the muscle fibers. To secure valid information on the influence of hypertrophy, it seemed necessary to rule out a factor which, as already noted, exerts a pronounced elevating influence on the level of creatine in the heart, namely nitrogen retention with its accompanying retention of creatinine and creatine. For this purpose 44 cases were selected covering the range of heart weights, but excluding all cases with nitrogen retention.

The cases were arranged according to heart weight

and divided into 7 groups. The heart weights ranged from 200 to 825 gm. The average creatine concentration of the left ventricle in the 7 groups were: 213, 244, 210, 196, 177, 152 and 140 mg. per 100 gm. in comparison with the normal average of 203 mg. per 100 gm. Similar changes were noted in the phosphorus and potassium, and the findings in the right ventricle paralleled those in the left. It will be noted that with the first increments in heart weight there is a quite definite elevation in creatine, but with further increments the values begin to fall and decline with each increment in heart weight, the final values being 20 to 35 per cent below normal.

not die in heart failure. In other studies we have had some cases of uremia which did not have marked nitrogen retention and did die in heart failure. This apparently was true of the cases studied by Gross and Sanberg[2], since they state: "In uremia associated with chronic congestive heart failure creatine concentration was reduced in all the muscles studied."

Indirect information regarding adenosinetriphosphate has been obtained on 24 human hearts, including 6 cases of congestive heart failure. The nitrogen of the purines convertible to oxypurines was determined, and from this adenine was calculated. In addition creatine and acid-soluble phosphorus were

TABLE II
Average Creatine, P and K Concentration in Cardiac Muscle in Myocardial Insufficiency and Other Conditions (mg. per 100 gm. of wet tissue)

	No. of Cases	Left Ventricle			Right Ventricle		
		Creatine	P	K	Creatine	P	K
Normal	13	203	194	285	165	160	219
Myocardial insufficiency	17	146	169	232	112	135	178
Cor pulmonale	4	217	186	271	136	132	166
Diabetes mellitus	3	200	197	272	126	144	194
Miscellaneous cardiac involvement	20	190	185	259	149	148	195
Uremia without heart failure	11	246	199	286	182	153	205

With the above background we are in a position to study and try to interpret the findings observed in myocardial insufficiency. It is believed that the findings obtained in this group are especially significant. Average data on 17 cases of myocardial failure are recorded in Table II, and similar data given on cases classified as miscellaneous cardiac involvement, cor pulmonale, diabetes mellitus, uremia and normals for comparison. Only those patients whose condition was clinically diagnosed as myocardial insufficiency and who showed evidence of progressive decompensation with hyperemia of the internal organs and edema of the extremities were included.

determined. From the data presented in Table III, it will be observed that in heart failure the left ventricle shows a decrease in this purine fraction along with the decrease in creatine and total acid-soluble phosphorus, but that this drop does not occur in the right ventricle, despite the fall in the creatine and total acid-soluble phosphorus. On the other hand it is significant that in pneumonia the adenine appears to be definitely decreased in the right ventricle, while the creatine and total acid-soluble phosphorus are all slightly elevated in the left ventricle.

SUMMARY. There is reasonably good evidence, direct and circumstantial, that phosphocreatine and

TABLE III
Average Adenine, Creatine and Total-Acid Soluble Phosphorus Content in Cardiac Muscle (mg. per 100 gm. of wet tissue)

	No. of Cases	Left Ventricle			Right Ventricle		
		Adenine	Creatine	TASP	Adenine	Creatine	TASP
Entire series	24	86	205	106	54	152	74
Heart failure	6	72	161	91	54	128	67
Tuberculosis	5	87	225	117	56	162	78
Pneumonia	8	90	222	110	48	160	75
Miscellaneous	5	91	211	107	63	161	78

As will be observed the average concentrations of creatine, phosphorus and potassium were decreased in both ventricles of the heart. In every case the creatine content of the left ventricle was below the normal level, varying from 16 to 52 per cent below the normal. In this series of cases there was also a definite reduction in the creatine content of the voluntary muscle (average 349 mg.) probably due in part to long enforced inactivity.

It would appear significant that the creatine and also the phosphorus and potassium, were definitely reduced in the right ventricle in cor pulmonale, while the values were normal (creatine slightly elevated) in the left ventricle. It is equally significant that there was an even greater creatine reduction in the right ventricle in diabetes mellitus, with essentially normal values for the left ventricle.

The observations in the cases of uremia without heart failure stand in contrast to the cases of myocardial insufficiency. Here, probably due in considerable part to the creatinine retention, the creatine concentration is definitely elevated in both ventricles, 20 per cent in the left and 10 per cent in the right. The values for phosphorus and potassium approach the normal. These observations suggest that the full maintenance of the creatine and other factors may help to explain why these patients did

adenosinetriphosphate, as potassium salts, play an essential role in muscular activity, or more specifically are vital agents in the transfer of chemical to mechanical energy for muscular work. In the very early stages of cardiac hypertrophy there appears to be an increase in the concentration of creatine, phosphorus and potassium, but with further hypertrophy all the values appear to fall and reach their lowest levels with extreme cardiac hypertrophy and heart failure. In cor pulmonale and diabetes mellitus there appears to be a definite fall in these three constituents in the right ventricle in comparison with nearly normal findings in the left ventricle. Adenine falls in the left ventricle in heart failure, and appears to be decreased in the right ventricle in pneumonia. While it has not been definitely established that heart failure is due to the decreased concentration of these apparently vital constituents, their evident role in the performance of muscular work would suggest some definite connection between their decreasing concentration and failure.

Victor C. Myers, Ph.D., D.Sc.
Cleveland, Ohio

REFERENCES

1. Myers, V. C.: Bull. New York Acad. Med., 18: 303, 1942.
2. Gross, H., and Sanberg, M.: Ann. Int. Med., 16: 737, 1942.
3. Wearn, J. T.: Bull. New York Acad. Med., 17: 754, 1941.